REMARKS

Prior to the present amendment, claims 1-7, 9-11, and 13- 25 were pending. Claims 8 and 12 are withdrawn from consideration due to a non-elected invention. By the present amendment, applicants have amended claims 1 and 8. Accordingly, claims 1-7, 9-11 and 13-25 are currently pending.

On page 2 of the Office action, claims 1-7, 9-11 and 13-25 were rejected under 35 U.S.C. §112, first paragraph for alleged lack of written description. According to the examiner, the claims were amended to state that each of the micelles comprise the first and second lipopeptide. However, the examiner reports that applicant has not pointed to support for where this limitation can be found in the specification. In addition, the examiner states that she is unable to locate support in the specification. The examiner requires that applicants indicate where support for the limitation is found.

Support for the limitation that the micelles of the present invention comprise (i) a first lipopetide comprising at least one CTL antigenic determinant and at least on lipid unit, and (ii) a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit can found in the specification as originally filed. See, *inter alia*, on page 5, lines 13-22 of the specification, which states the following:

> The **mixed micelles according to the invention, in other words comprising lipopeptides containing cytotoxic antigenic determinants and lipopeptides containing helper T antigenic determinants**, have the advantage of combining, wherein the same microvolume which can be assimilated by a single APC, a wide variety of CTL and HTL antigenic determinants, without their covalent combination being necessary, while respecting the required criterion of chemical definition. Micelles which

> each contain a single type of lipopeptide, containing a CTL antigenic determinant or an HTL antigenic determinant, do not result in an effective co-presentation corresponding to the induction of a strong effector response. *Emphasis added.*

From the above disclosure in the specification, applicants respectfully submit that the claim limitation is supported in the specification. Accordingly, applicants request that the rejection under §112 be reconsidered and withdrawn.

Claims 13, 14, 16 and 20 were rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement. The examiner contends that applicants' arguments and submission of two journal articles in the amendment dated December 4, 2001 were unpersuasive that the claimed vaccine would be effective.

The examiner acknowledges that Pialoux et al. (AIDS, 2001, 15:1239-1249) and Gahery-Seard et al. (J. Virology, 2000, 74:1694-1703) demonstrate that a CTL response is induced by the claimed micelle composition. However, the examiner contends that there is no data that would indicate the instant vaccine composition has therapeutic and/or prophylactic efficacy in HIV-infected subjects. Therefore, the examiner asserts that it would require undue experimentation to practice the claimed invention.

The examiner requires that applicants submit sufficient data that would indicate that the composition is efficacious within the HIV vaccine art.

Again, applicants continue to believe that the disclosures of Pialoux et al. (2001) and Gahery-Seard et al. (2000), discussed at length from pages 10-13 of the amendment dated December 4, 2001, provide ample evidence to convince one of skill in the medical

arts that the claimed mixed micelle or micro-aggregates are functional in inducing an immune response as claimed.

However, in order to expedite prosecution, applicants submit herewith two additional articles to support the efficacy of the claimed vaccine composition.

First, attached as exhibit 1, is a scientific article authored by some of the inventors of the present invention and published after the priority date of the claimed invention. The Gahery-Segard et al. article (J. Virology, 2003, 77:11220-11231) demonstrates that the claimed compounds induce a long-term specific immune response by the induction of long-term reactive $CD8^+$ T cells specific for HIV-1 virus antigens. See page 11229, first full paragraph, which states "the majority of positive responders induced and maintained multiepotopic $CD8^+$ T cell responses."

The authors further report on page 11230, last full paragraph, the following:

> Our results indicated that $CD4^+$ - and $CD8^+$-T-cell epitopes included in the HIV-1 lipopeptide are efficiently processed in humans. ... Moreover, the sustained multiepotopic HIV-1 $CD4^+$- and $CD8^+$-T-cell responses obtained in our clinical trial might have important implications also for immunotherapy....

Second, attached as exhibit 2, is a Levy et al. abstract authored by some of the inventors, and presented at the 10th Conference on Retrovirus and Opportunistic Infections held on September 18-21, 2003. The Levy et al. abstract titled "Immunological and Virological Efficacy of ALVAC-VIH 1433 and HIV Lipopeptides (Lipo-6T) Combined with SC IL-2 in Chronically HIV-infected Patients-Results of the

ANRS 093 Randomized Study" relates to a clinical study of the induction of an anti-HIV immune response in HIV-infected patients.

The authors state in the conclusion section the following:

> Vaccinated pts experienced a better control of HIV replication after stopping HAART. This effect is associated to the stimulation of a sustained and a polyepitopic HIV immune response.

Thus, these most recent results show that the claimed vaccine compositions are actually active against HIV, in HIV-infected patients.

Accordingly, applicants request that the rejection under §112 be reconsidered and withdrawn.

Claims 1-7, 9-10, 13-17 and 19-25 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Stuhler et al., Sastry et al. and Sugimoto et al. According to the examiner, Stuhler et al. discloses CTL and helper epitopes, and activation of a number of immune cell types. The examiner states Stuhler et al. does not teach palmitic acid residues. However, the examiner cites Sastry et al. for teaching palmitic acid residues and eliciting cell-mediated immunity with micelle compositions comprising an HIV protein attached to palmitic acid residues. Therefore, the examiner contends that it would be within the skill in the art to combine the method of stimulating helper, CTL, and APC immune response by combining the helper and CTL epitopes taught by Stuhler et al. in the micelle composition taught by Sastry et el. because the linked micelle epitopes would contact the same APC at the same time and the epitopes would not require a carrier molecule.

Applicants respectfully disagree that the claimed invention is obvious. Applicants have amended claim 1 to recite that the claimed composition comprise **more than one** first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit. Support for this amendment can be found in the specification as originally filed, *inter alia,* page 6, lines 3-14.

Stuhler et al. discloses *in vitro* induction of cytolytic T lymphocytes by incubating HLA-A2 positive peripheral blood mononuclear cells with a combination of HTL epitope and a CTL epitope.

Sastry et al. discloses induction of cytolytic immune response against HIV without the simultaneous induction of an antiviral antibody response (see page 700, line 2 et seq.)

Sugimoto et al. reports the adjuvant effect of a synthetic peptidoglycan.

Neither Stuhler et al., Sastry et al. nor Sugimoto et al. discloses or suggests the essential technical feature of the claimed invention, specifically a composition comprising **more than one** first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit.

In fact, Sastry et al. discloses administering a single peptide to mice. Thus, Sastry et al. only teaches the use of a single immunogenic determinant bearing peptide. Therefore, Sastry et al. clearly dissuades one of skill in the art from using a composition containing **more than one** first lipopeptide, as is required by the claimed invention.

As stated in the specification, micelles containing **more than one** first lipopeptide comprising at least one CTL antigenic determinant are advantageous compared to

methods disclosed in the prior art, such as those disclosed by Vitiello et al. (1995) wherein HTL and CTL units are combined covalently.

A demonstration of the effectiveness of the claimed composition for inducing a multiepitopic CTL response is shown in the application. See, *inter alia,* example 4 of the specification.

Further, the advantage of the claimed composition of micelles containing more than one lipopeptide comprising at least one CTL antigenic determinant is shown and discussed in Gahery-Segard et al. (2003). Gahery-Segard et al. (2003) on page 11229, first full paragraph, report that multiepitopic $CD8^+$ T cell responses are obtained with the claimed compositions. Further, page 11230, last paragraph state that "these lipopeptides have the potential to be generated in many different epitopes that can react with difference major histocompatibility complexes (MHCs), which make it possible to use this approach in individual patients, regardless of their MHC."

Thus, in contrast to compositions that would contain a single combination of a CTL antigenic determinant and a helper T antigenic determinant, the claimed composition of micelles can be widely used for inducing an effective multiepitopic cytotoxic immune response in a patient, regardless of the patient's MHC.

The above statement has been confirmed by the clinical trial which is disclosed in the abstract of Levy et al. (2003). There, a polyepitopic HIV immune response has been shown to effectively vaccinate HIV-infected patients who have stopped all medical treatment by HAART.

Accordingly, the claimed invention is not obvious over the cited references. Applicants respectfully request that the rejection under §103 be reconsidered and withdrawn.

Claim 11 was rejected under 35 U.S.C. §103(a) as allegedly obvious over Stuhler et al., Sastry et al. and Sugimoto et al. and further in view of Kramer et al. The examiner points to the Kramer et al. reference for the disclosure of the GAG 253 peptide as an immunogenic sequence and its use in detection assays and pharmaceutical compositions.

Applicants note that claim 11 is dependent on independent claim 1. Applicants have provided arguments to refute the rejection of claim 1 over Stuhler et al., Sastry et al. and Sugimoto et al. Accordingly, claim 11 is patentable at least for the same reasons that claim 1 is patentable.

Therefore, applicants respectfully request that the rejection under §103 be reconsidered and withdrawn.

Claim 18 was rejected under 34 U.S.C. §103(a) as allegedly obvious over Stuhler et al., Sastry et al., Sugimoto et al. and Kramer et al. and further in view of Shapiro et al. The examiner cites the Shapiro et al. reference for teaching use of two-dimensional magnetic resonance to aid in analyzing the conformation of micelle/peptide-receptor interactions.

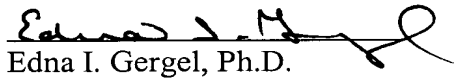
As discussed above, the combination of Stuhler et al., Sastry et al., Sugimoto et al. and Kramer et al. does not lead to the claimed composition comprising **more than one** first lipopeptide comprising at least one CTL antigenic determinant. The addition of the teachings of Shapiro et al. concerning the use of two-dimensional NMR fails to repair this defect.

Accordingly, applicants respectfully request that the rejection under §103 be reconsidered and withdrawn.

Applicants have also amended claim 25 in order to correct the dependency. No new matter has been added as a result of this amendment.

For all of the above reasons, applicants respectfully request allowance of pending claims 1-7, 9-11 and 13-25. If the examiner has any questions regarding this amendment, the examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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